UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE CELGENE CORPORATION SECURITIES LITIGATION	Case No. 18-cv-04772 (MEF) (JBC)

LEAD PLAINTIFF'S SUPPLEMENTAL STATEMENT OF DISPUTED MATERIAL FACTS PURSUANT TO LOCAL CIVIL RULE 56.1

Pursuant to Local Civil Rule 56.1, Lead Plaintiff AMF Pensionsförsäkring AB submits the following Supplemental Statement of Disputed Material Facts.[1]

A. FDA Guidance Sets Forth the Agency's Expectations Regarding the Content of an NDA

1. The U.S. Food and Drug Administration's ("FDA") expectations regarding the content of a New Drug Application ("NDA") are set forth in FDA guidance documents ("FDA Guidance") and Manuals of Policies and Procedures ("MAPPs"). PX 41 ¶ 17. The federal regulations governing NDAs state that the "FDA will maintain guidance documents on the format and content of NDAs to assist applicants in their preparation." PX 103. FDA Guidance is "prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products." PX 104 at 1; see also PX 40 at -851 (email from Michael Faletto ("Faletto"), Celgene's Executive Director of Regulatory Knowledge and Insights describing FDA guidance document as setting forth "requirements").

[1] Unless otherwise noted herein, all emphasis is added and all citations to "PX __" are to the exhibits to the accompanying Declaration of James E. Cecchi in Support of Lead Plaintiff's Response Pursuant to Local Civil Rule 56.1 to Defendants' Statement of Material Facts Not in Dispute and Lead Plaintiff's Supplemental Statement of Disputed Material Facts Pursuant to Local Civil Rule 56.1.

2. MAPPs, in turn, are "federal directives and documentation of internal policies and procedures." PX 105.

3. A drug sponsor that conducts a drug development program in a manner that is inconsistent with FDA Guidance and industry customs and practices creates a significant risk that the FDA will take adverse action on the drug's application. PX 41 ¶¶ 67-86; *see also id.* ¶¶ 16-22.

B. Mass Balance Studies Are Critical Studies Used to Understand the Metabolism of Drug Candidates

4. A human mass balance study—also referred to as an absorption, distribution, metabolism, and excretion ("ADME") study—is a study conducted during the drug development process that is used to identify and quantify the circulating parent drug and metabolites following the ingestion of a drug. Typically, a radioactive atom label is incorporated into the drug (usually carbon-14 or tritium) and then the radiolabeled products are analyzed through a chromatographic process. PX 9 ¶¶ 31, 61.

5. Mass balance studies are typically conducted prior to the initiation of Phase III clinical trials. As Baillie, et al. stated in a 2002 paper entitled "Drug Metabolites in Safety Testing," "it seems reasonable to expect that the sponsor would wish to develop an understanding of the metabolic fate of the drug candidate in humans ***prior*** to the initiation of large Phase III clinical trials," emphasizing that "the importance of the animal and human ADME studies [used to identify metabolites] cannot be overemphasized, the results of which need to be viewed in the context of all available pharmacology and toxicology data." PX 12 at 192. Penner, et al. similarly stated in a 2009 paper entitled "Human Radiolabeled Mass Balance Studies: Objectives, Utilities and Limitations" that "the metabolic fate of a drug candidate in preclinical species and humans is a ***key factor*** in new drug development, registration and ultimate use." PX 11 at 185-86.

6. The FDA's Guidance on Safety Testing of Drug Metabolites ("MIST Guidance"), issued in 2008, calls for "the identification of differences in drug metabolism between animals used in nonclinical safety assessments and humans ***as early as possible*** during the drug development process" and warns that "[t]he discovery of ***disproportionate drug metabolites*** late in drug development can potentially cause ***development and marketing delays***."[2] PX 106 at 3; *see also* PX 107 at 42 (then-Celgene Vice President, Matthew Lamb ("Lamb"), Global Head of Regulatory Affairs - I&I, testifying that "[A]ctive metabolites . . . could be tied to the efficacy of the molecule and the desired effects you're looking for and/or off-target effects as well, which may be tied to safety aspects," so "***it is important to make sure that you understand the full metabolic profile***"); *id.* at 62-63 (testifying that a delay in the filing of the NDA "would certainly be one of the possible implications" of discovery of the 2273 metabolite (defined below) because "[t]here was a considerable amount of work to be done to understand the overall impact").

7. As Baillie subsequently explained in a 2009 paper, the FDA's MIST Guidance "underscores the need for sponsors to conduct studies on the metabolic fate of drug candidates ***at an early stage of clinical development, such that issues of disproportionate human metabolites may be addressed prior to the initiation of large-scale clinical trials***." PX 108 at 263-64. Baillie further noted that mass balance studies utilizing a "radiolabeled drug" to identify metabolites are "generally [ ] accepted as the 'gold standard' method for defining the fate of a drug candidate in man." *Id.* at 264. Penner, et al. similarly noted that radiolabeled mass balance studies are "viewed as the ***primary source of data on human metabolites from which a decision can be made***

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[2] A disproportionate metabolite is a metabolite that is "formed in humans but not generated in experimental animals used in drug testing, or formed in humans at disproportionately higher levels than in animal test subjects." PX 9 ¶ 53.

regarding the need for further safety assessment in preclinical species," emphasizing that "[h]uman radiolabeled mass balance . . . studies are ***required*** by regulatory authorities for the registration of a new drug and, therefore, are an integral part of the majority of drug development programs." PX 11 at 186.

C. Celgene Belatedly Conducted the Ozanimod Mass Balance Study in October 2016, Just Fifteen Months Prior to the Planned NDA Submission

8. In accordance with the FDA's MIST Guidance, as well as industry practice and customs, Celgene should have conducted the Ozanimod mass balance study prior to October 2016 (the actual initiation date of the study) and prior to the initiation of the Phase III clinical studies for Ozanimod. PX 14; *see* PX 107 at 44 ("a typical human mass balance study would be done in the latter part of the ***Phase I*** development phase of a program"); *see also* PX 9 ¶¶ 59-61, 73.

9. In a draft "Q&A" document that Jean-Louis Saillot, M.D. ("Saillot") (Vice President of Project Leadership, Regulatory Affairs, and Clinical Pharmacology at Receptos) sent to Jonathan Tran ("Tran") (Executive Director of Clinical Pharmacology at Receptos), Saillot acknowledged that the "human mass balance study" was conducted "***very late*** in the development of ozanimod." PX 109 at -548; *accord* PX 107 at 43 ("***it was late*** for the conducting of a human mass balance study"). Saillot further stated: "Such studies are usually planned before or during Phase 2, so that the metabolic profile is completely understood before full clinical development and finalization of the non-clinical safety package, including carcinogenicity studies when needed. ***There is clear regulatory guidance on when such studies should be done, which was not followed***." *Id.*; *see also supra* ¶ 6; PX 110 at -586 ("we should have known about 2273 before").

10. During the Class Period, Saillot reported directly to Defendant Phillippe Martin ("Martin"), Celgene's Vice President of Leadership & Project Management – Immunology. PX 16 at 9, 13.

D. Disproportionate Metabolites Require Additional Safety Testing That Must Be Completed Prior to Submitting an NDA

11. Pursuant to FDA's MIST Guidance, disproportionate metabolites and metabolites "formed at greater than 10 percent of parent drug systemic exposure at steady state" can raise a safety concern and require safety testing, including general toxicity studies, genotoxicity studies, embryo-fetal development toxicity studies, and carcinogenicity studies. PX 106 at 3, 5-6; *see also id.* at 3 ("Generally, metabolites identified only in human plasma or metabolites present at disproportionately higher levels in humans than in any of the animal test species should be considered for safety assessment."); PX 111 at 6 ("Nonclinical characterization of a human metabolite(s) is . . . warranted when that metabolite(s) is observed at exposures greater than 10 percent of total drug-related exposure and at significantly greater levels in humans than the maximum exposure seen in the toxicity studies."); PX 107 at 60-61 ("If the metabolite accounts for greater than 10 percent of the parent, it is deemed a major acting metabolite, which then does ***require some additional characterization*** to be done.").

12. FDA Guidance provides that if a metabolite composes the majority of the total drug-related human exposure, the safety multiple achieved in the pivotal toxicology studies must be 1.0 or greater. PX 112 at 5 ("characterization of metabolite toxicity would generally be considered adequate when animal exposure is at least 50 percent the exposure seen in humans," but "[i]n some cases, ***for example when a metabolite composes the majority of the total human exposure***, ***it is appropriate for exposure to the metabolite in animals to exceed that in humans***. . . . In this latter case it is important to achieve a higher exposure to the metabolite in animals because this metabolite constitutes the bulk of human exposure."); *see also* PX 48 at -092 (July 20, 2017 email from David Jacobson-Kram ("Jacobson-Kram") to Tran quoting this guidance).

13. FDA Guidance provides that, in connection with an NDA submission, a drug sponsor must submit full clinical study reports ("CSRs"), including bioanalytical validation reports containing long-term stability ("LTS") data covering all samples that have been tested (or "assayed") for a given analyte.[3] PX 113 at 13 ("Assays of all samples of an analyte in a biological matrix should be completed within the time period for which stability has been demonstrated."); *id.* at 16-17 ("The validity of an analytical method should be established and verified by laboratory studies, and documentation of successful completion of such studies should be provided in the assay validation report. . . . Documentation . . . should include . . . [a] description of ***stability studies and supporting data***."); *see also id.* at 8 ("All experiments used to make claims or draw conclusions about the validity of the method should be presented in a report (method validation report)."). As explained by Plaintiff's FDA regulatory expert, Dr. Nicholas Fleischer, "[c]onsistent with the Bioanalytical Method Validation Guidance, the FDA considers a full clinical study report (including for pharmacokinetic studies) to be one that includes bioanalytical validation reports documenting that LTS has been established for 'all samples' that were analyzed in the study." PX 44 at ¶ 26 (quoting Bioanalytical Method Validation Guidance); *see also* PX 41 at ¶¶ 27-28, 30-35, 69-73; PX 114 at 309-10 ("[v]alidation of analytical methods should be performed to support pharmacokinetic, bioequivalence, and related studies in a new drug application"); PX 107 at 38-39 (Lamb testifying that the FDA expects that an NDA include full CSRs, which typically include bioanalytical and validation reports); *id.* at 99 ("completed CSRs . . . would include stability data . . . as part of those reports.").

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[3] An analyte is a substance whose chemical constituents are being identified and measured.

E. An NDA That Lacks Bioanalytical Validation Data Is Subject to a "Refusal to File" by the FDA

14. As provided in FDA Guidance, absent agreement from the FDA, an NDA must be complete at the time of submission by the drug sponsor. PX 39 at 3 ("Unless the applicant and the FDA have agreed at the presubmission meeting to delayed submission of certain components of the application, the FDA expects applications to be complete at the time of submission."). Incomplete applications are subject to a "refusal to file" ("RTF") by the FDA. PX 40 at -856 ("Applications are expected to be complete as agreed upon by the FDA and the applicant at the presubmission meeting. ***Incomplete applications*** . . . ***will be subject to an RTF decision***."); PX 115 at 10 ("If no agreement on the type of study reports to be submitted [i.e., full or abbreviated] has occurred prior to submission and the Agency finds the information submitted to be insufficient on its face to evaluate safety and/or effectiveness, this inadequacy may serve as a basis to refuse to file the application (21 CFR 314.101(d)(3)").

15. As described in FDA Guidance, an RTF indicates the FDA's rejection of an NDA based on facial inadequacies identified through a summary review of the NDA's contents. PX 17 at -179 (FDA may refuse to file an NDA when it determines that the application is "deficient, on its face, in a way that precludes a complete review."); *see also* 21 C.F.R. § 314.101(d)(3) (setting forth circumstances under which RTF may be issued).

16. Some review issues may result in the FDA issuing an RTF letter. PX 39 at 4 ("During the filing review, FDA staff may also identify certain review issues that result in a refuse to file pursuant to § 314.101(d)(3) and other authorities . . . . some review issues may render an application incomplete and may therefore result in a refusal to file.").

17. As stated by the FDA, an example of a deficiency that can support an RTF action is the failure to include bioanalytical validation reports. PX 40 at -868, -871 ("examples of

complex and significant deficiencies that may provide support for an RTF action" include the "***[f]ailure to provide bioanalytical method validation . . . for the bioanalytical assays used to determine drug concentrations in biological matrices***").

F. Prior to April 27, 2017, Defendants Had Substantial Evidence of a Disproportionate Metabolite That Jeopardized the Already "Back-Loaded" NDA Submission Timeline

18. At the time Celgene initiated the mass balance study in October 2016, it recognized that the work plan required to meet the December 2017 Ozanimod NDA filing commitment was "***heavily back-loaded***" and put a "[h]uge workload on [the] team with little time for delays/errors." PX 116 at -454.

19. As early as January 2017, Celgene recognized the likelihood of a new Ozanimod metabolite being identified based on the preliminary results of the mass balance study. As Dr. Frederick Guengerich, Plaintiff's toxicology and chemistry expert, explained, by January 2017, Celgene had evidence "that there was a defect in the mass balance study, which is an indication of an extra metabolite that's not been accounted for. That's what the purpose of the mass balance studies is." PX 19 at 74-76.

20. The minutes from the January 12, 2017 meeting of the Ozanimod Multiple Sclerosis ("MS") Team stated that Celgene was planning a formal risk assessment for the first quarter of 2017, and the first item to be addressed was: "Identification of a new metabolite in the human mass balance study." PX 18 at -643. These meeting minutes further stated that "[i]f a significant new metabolite is identified, then ***we will not have sufficient toxicology [studies] to support the [NDA] submission***." *Id.*

21. The FDA's March 2, 2017 written responses, which were distributed to Martin, Saillot, Gerlee Thomas ("Thomas") (Director of Regulatory Affairs at Receptos), David Kao ("Kao") (Executive Director, Regulatory Affairs at Receptos), Brett Skolnick ("Skolnick")

(Executive Director, Clinical Development at Receptos), Susan Meier-Davis ("Meier-Davis") (Senior Director in Pre-Clinical Sciences at Receptos), and Tran, observed that "several Phase 1 studies are still ongoing," including RPC01-1001, RPC01-1904, PRPC01-1906, and RPC01-1910, and advised Celgene that "***[f]ull Clinical Study Reports are needed for these clinical pharmacology studies at the time of the NDA submission***." PX 20 at -055.

22. The MS NDA Submission Dashboard for the week of March 27, 2017, which was distributed to Martin, Saillot, Kao, Skolnick, Jeffrey Kopicko ("Kopicko") (Executive Director of Biometrics at Receptos), Esther Martinborough ("Martinborough") (Executive Director of Research in Computational Chemistry at Receptos), and Richard Aranda ("Aranda") (Vice President of Clinical Development at Receptos), among others, confirmed that Celgene viewed the "[p]otential to identify a new metabolite" through the mass balance study as a "key issue[]" and noted that "[p]reliminary (chromatographic) data from plasma samples in the [mass balance study] is expected by the end of this week to possibly provide a clue about any potential new metabolite for [Ozanimod]." PX 21 at -071.

23. A March 28, 2017 presentation sent from Karen Zoller ("Zoller"), Senior Director, Program Management, to Saillot confirmed that the "***[c]urrent tox data package would not be sufficient*** if a new metabolite is identified in the [mass balance study]," acknowledging this as a "***Potential Risk[] to the Ozanimod Submission***." PX 22.

24. The minutes from the April 3, 2017 Ozanimod MS Team Meeting attended by Saillot, Skolnick, Tran, Meier-Davis, Kao, and Thomas, among others, stated that "[c]hromatograph results from the plasma samples collected in the [mass balance study] showed results that require follow-up activities, including whether this may be evidence for a metabolite that was not seen in the non-clinical studies." PX 23 at -741. These minutes further stated that

the Ozanimod MS Team was "track[ing] status of this work on a weekly basis," and that a "new-cross functional team" was "established led by [Martinborough] and [Meier-Davis] . . . to oversee investigation into this finding and mitigate any potential risks." *Id.*

25. A PowerPoint presentation that Martinborough sent to Martin and Saillot following a meeting on April 24, 2017 stated the following with respect to the data from the mass balance study: "***It appears that this new peak is real***." PX 24 at -581. The presentation further noted: "[W]e are assuming that it is a single peak >10% [of Ozanimod's systemic exposure]." *Id.* The presentation expressly noted the possibility that Celgene would need to delay the NDA submission by ***eight months*** (to September 2018) in order to perform a non-clinical rat carcinogenicity study on the new metabolite (the "Metabolite" or "2273").

G. Between April 27 and July 27, 2017, Additional Evidence Confirmed the Presence of the Metabolite That Would Delay Submission of the NDA Beyond 2017 or Else Pose a Major RTF Risk

26. By July 25, 2017, Defendants had further substantial evidence of the Metabolite and the Metabolite's impact on the timing of the NDA submission, in addition to the evidence set forth in ¶¶ 18-25 above.

27. On May 16, 2017, Saillot emailed Martin about the risks posed by the new data from the mass balance study and implored him to inform Defendant Smith:

> You're going to be mad at me for this one . . . Sorry. But I feel really strongly about this. You need to let Scott know. For the following reasons: ***In the best case scenario the December timeframe [for filing the NDA] is extremely optimistic.*** Anything that slows down the progress (challenges in identification of the components of the peaks, etc…) will put that timeline in jeopardy. We can leverage his being brought up to speed to ask for the mobilization of the resource[s] that we talked about to be assigned to the project. As noted below, this can be position[ed] as a heads up – That we have this finding and we need to address it in the best way (ranging from being able to explain it away, ***to putting this in the best context to negotiate any additional actions with the Agency***) . . . .
>
> I do not see any down side. ***Painful as the potential bad news is shared***, but better moving forward (just focusing on getting the job done and not being distracted). I

> can assure you that the team will not let this investigation slow down their progress (not on my watch). . . .

PX 27 at -279. Martin responded to Saillot that they would discuss the Metabolite issue the following day with the Receptos Executive Committee. *Id.*

28. In a May 30, 2017 email to Saillot, Martinborough, and Meier-Davis, among others, Tran requested additional information regarding the Metabolite and "emphasize[d] the importance and urgency of getting resolution to this issue because it could potentially require us to go back and amend the completed clinical study reports for 6 Phase 1 studies and making changes to the ongoing clinical study reports for 3 Phase 1 studies." PX 28 at -518. As Tran explained: "This is a major task . . . . Most importantly, ***these changes could have a significant negative impact on the NDA deliverables and timeline***." *Id.* at -518-19.

29. On June 1, 2017, Tran emailed David Wilson ("Wilson"), the clinical bioanalytical lead at Receptos, and asked if there would be any issue using old plasma samples from the previously conducted clinical studies to measure and analyze the Metabolite as required by FDA Guidance rather than conducting the necessary studies anew. PX 29 at -572. Wilson responded that Celgene lacked sufficient LTS data to validate the Metabolite for the RPC01-1001 clinical study (the "1001 Study") due to the age of the retained plasma samples collected during the study. *Id.* at -571. He explained that if Celgene were to rely on 2273 data from the 1001 Study, "LTS becomes a real concern" as the FDA "won't consider the data as validated." *Id.* As Wilson further stated in his response:

> ***Right off the bat, stability would be a main concern*** . . . . if we use . . . [the] 1001 [Study], LTS becomes a real concern. There will be some samples that you won't get validated LTS for until nearly our anticipated PDUFA time (or beyond) [i.e., 12 or more months after the NDA submission]. ***So the agency won't consider the data as validated***. If stabilizers are required in the plasma to keep the compound from converting, no existing study will work.

Id. at -571-72.

30. During a June 1, 2017 meeting of the Receptos Executive Committee, Tran presented a series of slides entitled, "Impact of new peak on Clinical Pharmacology Strategy"—the "new peak" being a reference to the Metabolite. PX 30 at -872-80. This presentation stated: "***Primary concern: PK [pharmacokinetic] sample stability. Regulatory agencies will not consider data as validated due to lack of long-term stability (LTS) data***." *Id.* at -874.

31. On June 6, 2017, Wilson emailed Tran as follows:

> You had requested to know how much LTS we needed for a few studies to cover 2273 analysis. . . . Some thoughts for you:
>
> - Assuming M[ethod] V[alidation] completes in late September and we jump straight to [the] 1001 [Study], ***you'll need about 15 months LTS to cover this study***.
> - We don't have sufficient sample volume to analyze 201A.
> - [The] 201B and 301 [Studies] will need ~4 and 3 years LTS.
> - I've added a slide to my weekly update to track this stuff.

PX 31 at -786.

32. In connection with an Ad Hoc Executive Committee meeting on June 15, 2017, Tran prepared a presentation titled, "A Phase 1 study to evaluate PK and PD of Ozanimod and active metabolites following multiple dosing regimens (RPC01-1911)." PX 32 at -020-37. The invitees for this meeting included Martin, Saillot, Martinborough, Aranda, Kao, Thomas, and Tran, and the presentation was sent to Martin prior to the meeting. *Id.* at -019. Tran's presentation stated that "RP112273 is pharmacologically active and more potent (> 10-fold) than Ozanimod." *Id.* at -022. The presentation further stated: "RP112273 is likely the major and active moiety accountable for most of ozanimod's efficacy and/or safety . . . . ***Adequate characterization of RP112273 PK and PD properties are required by regulatory agencies***," including "[a]nalytical: Information on the ***stability*** of the analyte . . . ." *Id.* at -023; *see also* PX 107 at 43 ("[i]t's important

to characterize the metabolites"). Tran's presentation further emphasized that the test results must be "considered validated by regulatory (i.e., with long-term stability data)," and that "results are not considered validated due to lack of long-term stability data for PK samples ***at the time of filing [the NDA]***." *Id.* at -034, -037.

33. On July 5, 2017, Kao provided Saillot and Thomas with draft language for Celgene's pre-NDA meeting request to the FDA which acknowledged that Celgene would not have complete data for the Metabolite at the time of the planned NDA submission. PX 55. Specifically, Kao wrote to Saillot and Thomas: "As we discussed, here is some draft wording that we could consider to include in the Mtg Request Doc." *Id.* at -827. Kao proposed the following text:

> **PURPOSE OF MEETING**. . . . Celgene is also seeking FDA feedback and agreement on our proposed plans for the nonclinical qualification and PK/PD characterization of 112273, a recently-identified, active major metabolite of Ozanimod. Specifically, Celgene would like to obtain FDA confirmation that it would be acceptable to provide certain data regarding 112273 during the NDA review period [i.e., after the NDA submission] without delaying the PDUFA performance goal date, on the basis that Phase 3 clinical trial data are already available and support the safety and efficacy of Ozanimod in RMS [relapsing multiple sclerosis] patients.

Id. at -828.

34. In a July 6, 2017 email to Meier-Davis, among others, Tran stated that Celgene would not have "the actual human exposure [for 2273] until end of August/early September." PX 53 at -434.

35. On July 17, 2017, Tran gave a slide presentation to Martin and the Receptos Executive Committee entitled, "Clinical Pharmacology Strategy for RP112273 to support NDA submission and review." PX 56 at -178-94. On a slide titled "Summary of available Clinical Pharmacology data for Ozanimod at NAD [sic] submission (Dec 2017) and during NDA review (2018)," Tran informed Martin and the Executive Committee that Celgene would have "***[l]imited***

PK characterization of RP112273 in RMS patients (with no long-term stability data)" at the time of the NDA submission in December 2017. *Id.* at -194. This presentation was sent to Martin. PX 57.

36. A "Q&A" document drafted by Saillot and sent to Martin on July 17, 2017 posed the question: "What is the impact on the [NDA] submission [of the Metabolite discovery]?" The response stated: "***Unaddressed this would lead to a Refusal to File by FDA***." PX 15 at -638; *see also* PX 54 at -870. This document further stated: "The team is putting together a package with the available preliminary data and preparing for a meeting with FDA to negotiate submission of the NDA within the original timeframe, with agreement for additional data to be submitted during the review period . . . ." PX 15 at -638. The document noted that the "[b]est case" scenario was that the FDA would "accept submission within original timeframe," but also acknowledged the "[p]ossible scenario" that the FDA would "request submission of additional clinical Pharmacology and/or non-clinical safety data," causing the NDA submission to be "delayed by 1-2 Quarters" into the "1[st] H[alf] 2018." *Id.*

37. On July 25, 2017, Martin sent Smith and Curran an email stating that the "human mass balance study revealed a new disproportionate metabolite RP112273 (>10% of total drug related exposure) which was not previously detected in preclinical species," and that the "risk of a new metabolite[] was identified by the team in December 2016." *Id.* at -045. PX 3 at -045. Martin further stated that: "A lot of work remains to be done in a very short period of time ***in order to keep the submission on schedule***. Team integrity/cohesion (all functions are impacted from research to marketing) & focus over the next year and a half . . . are of ***critical importance***." *Id.* As Martin explained:

> As per FDA guidance on safety testing of metabolites (2016), metabolites present at disproportionately higher levels in humans than in any of the animal test species

> should be considered for (non-clinical) safety assessment. Human metabolites that can raise a safety concern are those formed at greater than 10 percent of parent drug systemic exposure at steady state. Since RP112273 is the major (>10-fold higher in exposure compare to the parent ozanimod) and pharmacologically active, ***adequate characterization of Clinical Pharmacology properties of RP112273 is required by regulatory agencies***.

Id. at -045-46; *see also* PX 107 at 47-48 (agreeing with Martin's statement that "adequate characterization of Clinical Pharmacology properties of RP112273 is required by regulatory agencies"); PX 117 at -683-84 (July 27, 2017 email summarizing discovery of the metabolite as "***material information*** being shared on a need-to know basis" that was known by Martin and had already been shared with Smith, Curran, Maria Palmisano ("Palmisano"), Celgene's Corporate Vice President of Clinical Pharmacology, and via Curran, Jay Backstrom ("Backstrom"), Celgene Chief Medical Officer.

H. Between August and October 2017, Further Evidence Confirmed That the Metabolite Required Additional Testing or Else Posed a Major RTF Risk

38. Beginning in early August 2017, Martin, Saillot, Kao, Backstrom, and Lamb, among others, participated in regular "touch base" teleconferences to discuss the progress of the Ozanimod NDA submission. PX 66 at -369. Lamb testified that these "touch base" meetings were "important" because "there was a lot of work to be done between that time point in August and the subsequent NDA submission." PX 107 at 67.

39. By October 26, 2017, Defendants had further substantial evidence of the Metabolite and the Metabolite's impact on the timing of the NDA submission, in addition to the evidence set forth in ¶¶ 18-37 above.

40. A slide deck that Wilson sent to Tran on August 1, 2017 confirmed that Celgene needed between approximately one and three years of LTS data to cover the samples from several Phase I and Phase III clinical pharmacology studies—data that Celgene would not have by

December 2017 when it planned to submit the NDA. PX 58 at -869. On August 10, 2017, in advance of the next day's I&I Regulatory Affairs monthly meeting, Saillot circulated a set of slides and wrote that he would "prefer that we only present these on WebEx rather than circulate given the ***sensitivity around this topic***." PX 118. The slides included under the heading "Bioanalytical," a reference to the need to "Develop and validate human plasma method for the analysis of RP112273" and warned that "***Incomplete Clinical Pharmacology package can potentially lead to Refusal to File***." *Id.*

41. On September 18, 2017, Wilson sent Tran a slide presentation with updated long-term stability calculations for the previously conducted studies of Ozanimod. PX 59. Wilson's presentation indicated that Celgene would not have sufficient LTS data to include in the NDA if it were to be submitted by the target of year-end 2017. Specifically,

- Celgene needed 508 days of LTS data for Study 1904, which would not be completed until **December 15, 2018**;
- Celgene needed 384 days of LTS data for Study 1906, which would not be completed until **August 13, 2018**;
- Celgene needed approximately 3 years of LTS data for Study 301, which would not be completed until around **January 2020**;
- Celgene needed approximately 5 years of LTS data for Study 201A, which would not be completed until around **August 2022**;
- Celgene needed approximately 2 years of LTS data for Study 1902, which would not be completed until around **June 2019**;
- Celgene needed approximately 1.75 years of LTS data for Study 1905, which would not be completed until around **March 2019**;
- Celgene needed approximately 1.5 years of LTS data for Study 1908, which would not be completed until **January 2019**; and
- Celgene needed approximately 4 years of LTS data for Study 201B, which would not be completed until **July 2021**.

Id. at -686.

42. On September 19, 2017, Tran provided Meier-Davis and Martinborough with the updated human exposure value for the Metabolite. PX 36. This new data established that the actual human exposure was 155,716 pg*h/mL, more than double the July 2017 estimate of 75,410 pg*h/mL. *Id.* at -845-46.

43. On October 19, 2017, Lamb forwarded to Florence Houn ("Houn"), Celgene's Vice President of Global Regulatory Science, a copy of the draft "Briefing Book" that is customarily submitted to the FDA in advance of the scheduled pre-NDA meeting with the goal of reaching agreement with the FDA on the planned course of action for submitting the NDA. PX 119. The draft Briefing Book contained Celgene's proposal to submit LTS data for the Metabolite after submitting the NDA in December 2017. PX 120 at -272-73. In his email, Lamb stated: "Personally, I don't feel the package is ready for submission and requires substantial rework." PX 119 at -394. Lamb confirmed in his testimony that his reaction to the document was that Celgene should "wait for the Ozanimod NDA submission until [they]'ve completed the studies and CSRs [he] identified." PX 107 at 88-92. After reviewing the document, Houn commented: "I don't see the rationale for the delayed metabolite characterization submission by 4 months with the other late CSR submissions." *Id.*

44. In an October 19, 2017 email, Ted Reiss ("Reiss"), Celgene's Corporate Vice President, Head of I&I Clinical Research and Development, provided his comments on the draft Briefing Book to Aranda, which were subsequently forwarded to Saillot, Tran, and Palmisano. PX 121. Reiss expressed concerns about the description of the metabolite, stating: "***It seems like you are going over board to sell a concept that the FDA will not buy anyway***—be careful with your credibility. . . . From my point of view this would need a lot of work. There is a lot of 'happy

language' and minimizing of tolerability issues." *Id.* at -310-11. Reiss also mentioned that "Matt [Lamb] had delivered similar comments." *Id.* at -310.

45. On August 7, 2017, the *Journal of Clinical Pharmacology in Drug Development* published an article sponsored by Celgene and authored by Tran and several other Celgene employees entitled "Cardiac Safety of Ozanimod, a Novel Sphingosine-1-Phosphate Receptor Modulator: Results of a Thorough QT/QTc Study." PX 122 at 263. The article stated that "Metabolism studies in animals identified 3 pharmacologically active metabolites (RP101988, RP101075, and RP101442) that have similar S1P selectivity and potency in vitro to ozanimod" and described the characteristics of these three metabolites. *Id.* at 264. However, the article did ***not*** disclose the discovery of 2273, notwithstanding that it was a pharmacologically active metabolite that accounted for 89% of the total exposure. PX 37 at -656.

I. Celgene's Pre-NDA Submission to the FDA Acknowledged That It Lacked the Required LTS Data and Sought Permission to File an Incomplete NDA

46. On October 27, 2017, Celgene submitted the Briefing Book to the FDA which acknowledged that Celgene would not have the required LTS data at the time of the planned NDA submission at year-end 2017 and sought agreement from the FDA that its plan to submit incomplete data would be acceptable. PX 60 at -561. [NEW] Martin reviewed a draft of Celgene's Briefing Book before it was submitted to the FDA on October 27, 2017. PX 2 at 175-76. The Briefing Book set forth its purpose, in relevant part, as follows:

> Celgene is also seeking feedback and agreement on the data for the nonclinical qualification and clinical pharmacokinetics (PK) and exposure-response characterization of RP112273, a disproportionate active metabolite of ozanimod. ***Specifically, Celgene would like to obtain FDA agreement that it would be acceptable, given the scope of the information included in the initial NDA, to provide additional clinical pharmacology data regarding RP112273 early in the NDA review period***, on the basis that phase 3 clinical study data are already available that support the safety and efficacy of ozanimod in patients with RMS.

Id. The Briefing Book set forth three questions regarding the acceptability of the data Celgene proposed to submit with the NDA by the end of the year:

- **Question 3:** Does the Agency agree that the proposed nonclinical package, including the evaluation of major metabolites, is adequate to support the filing for the registration of ozanimod?

- **Question 4:** Does the Agency agree that the overall proposed clinical pharmacology package, including the additional information planned to be provided early in the NDA review, is acceptable and supports the filing for the registration of ozanimod?

- **Question 5:** Does the Agency agree with Celgene's proposed timing for the bioanalytical [LTS] data package for the recently-identified major and active metabolite RP112273?

Id. at -579.

47. In the Briefing Book, under the heading "**Supportive Information for Question 5**," Celgene stated that it would ***not*** have the required LTS data by the time of the anticipated NDA submission in December 2017 and proposed to submit the additional required data beginning six months after the December 2017 submission and at regular intervals thereafter:

> A liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for the analysis of RP112273 has been developed and validated. . . . The method was validated according to the FDA Guidance on Bioanalytical Method Validation (2001) with consideration that samples from the previously completed clinical studies will be analyzed for RP112273 concentrations. For this reason, validation with greater short-term stability than is typical (ie, ≥ 5 freeze-thaw cycles and ≥ 24 hours bench top stability) and ***long-term storage stability (LTS) assessments (-20°C and/or -70°C, as appropriate) is ongoing as required to cover samples from the previously completed clinical studies.*** A method validation report will be provided following completion of core validation activities . . . . ***Validation report addenda will be prepared following completion of LTS assessments at intervals of approximately 1, 6, 12, 15, 18, 24, 30, and 36 months***. . . .
>
> Celgene plans to provide bioanalytical data as follows:
>
> **In the NDA Submission:** . . . ***As noted above, the validation report for RP112273 . . . will not include LTS assessments*** . . . .
>
> **By the 120-day safety update:** . . . Addendum to RP112273 plasma assay validation report . . . to include . . . some ongoing LTS assessments . . . .

Subsequent updates: ***Ongoing LTS assessments to cover required analysis*** . . . .

Id. at -684-85.

48. At the time of Defendants' October 26 and 28, 2017 statements, Defendants did not know whether Celgene's proposal to submit LTS data after the targeted NDA submission in December 2017 would be acceptable to the FDA. PX 60 at -561.

49. Prior to Celgene's Investor Event at the MSParis2017–7th Joint American-European Committee for the Treatment and Research in Multiple Sclerosis on October 28, 2017, Martin received and reviewed information concerning the Metabolite and the Metabolite's impact on the timing of the Ozanimod NDA submission. *See supra* ¶¶ 18-48; *see also* PX 124 at Response Nos. 2, 3 (Martin relied on "information he received from the Ozanimod project team, including Jean-Louis Saillot, Jonathan Tran, Esther Martinborough, David Kao, Susan Meier-Davis, and Gerlee Thomas"); PX 125 at Response No. 10 (this "statement was informed by numerous documents, meetings, correspondence, and discussions relating to Ozanimod throughout 2017").

J. The FDA Rejected Celgene's Proposal to Submit an Incomplete Ozanimod NDA, As Celgene Had "Expected"

50. After submitting the Briefing Book on October 27, 2017, Defendants continued to flag deficiencies regarding the safety testing for the Metabolite. In a document circulated by Kao on November 9, 2017, Celgene acknowledged that the exposure multiples were "insufficient" because they were below the 1.0 threshold. PX 110 at -590.

51. Defendants also internally acknowledged the likelihood that the FDA would reject Celgene's proposal to submit the incomplete NDA by year-end 2017. On November 20, 2017, Lamb emailed Curran about the possibility of using a priority review voucher ("PRV") which is a mechanism for a new drug applicant to expedite the FDA's review of an NDA:

> If . . . following the pre-NDA meeting, ***the FDA makes a strong recommendation that we shouldn't submit the NDA until we have all the information on the***

> ***metabolite available and we decide to wait until March-April 2018 to submit the NDA***, then I think it is fair to utilize a PRV [Priority Review Voucher]. This would allow for an approval in a similar time frame as if we had submitted the NDA in Dec[ember 2017].

PX 61 at -701. Six minutes later, Curran responded to Lamb: "***Agree***." *Id.*

52. Lamb also emailed Martin, Curran, and Saillot on November 20, 2017 regarding the use of a PRV:

> We've been approached about the potential sale of a Priority Review Voucher (PRV). . . . ***If*** . . . ***under the situation where the review division makes a strong recommendation to only submit the NDA when the additional information on the metabolite is available and the team decides to wait until early next year to submit***, I think it would be fair to consider [ ] a potential priority review . . . . Do you agree? If yes, and if FDA makes it clear that we should only submit once we have the complete metabolite information included in the NDA, it would be good to gauge the division's preliminary thoughts about the merits of a priority review . . . . [t]his could then inform thoughts around the use of a PRV.

PX 62 at -358-59. Saillot responded to Martin, Curran, and Lamb later that day:

> I must say that the team had discussed the option of trying to negotiate a priority review based on the same elements you highlight below in case the FDA were to ask us to delay the filing. . . . The writing of the briefing book was along these lines (addressing an unmet need), but short of mentioning the priority review. . . . ***I believe the highest risk is in our non-clinical safety argument (particularly the carcinogenicity)***. I am not sure how a priority review would best play in that scenario . . . .

Id. at -358.

53. On November 20, 2017, Curran emailed Smith regarding the potential use of a PRV:

> We have been approached about the opportunity to purchase a Priority Review Voucher (PRV). In the situation that the FDA doesn't accept the proposed Ozanimod strategy it would potentially enable us to keep the current timeline. The team is working up some scenarios to assess the value over Ozanimod's lifetime.

PX 63 at -009.

54. In a November 21, 2017 email to Reiss, Lamb stated: "If FDA does not agree with this [total agonist] approach, RP112273 will not be qualified across all tox studies." PX 126 at -471.

55. In its November 21, 2017 Preliminary Meeting Comments, the FDA informed Celgene that it needed to demonstrate that safety multiples of 1.0 or greater for 2273 had been achieved in the nonclinical studies. In response to **Question 3**, which asked, "Does the Agency agree that the proposed nonclinical package, including the evaluation of major metabolites, is adequate to support the filing for the registration of ozanimod?", the FDA did not agree, and cited the ICH M3(R2) guidance and Q&A, stating:

> You should ensure that all circulating major human metabolites (i.e., ≥ 10% of total circulating drug related material) have been adequately assessed in the nonclinical studies (see ICH M3(R2), January 2010; ICH M3(R2) Q&A, February 2013) . . . .
>
> Metabolite RP112273 is stated to account for 89% of total drug-related exposure in humans; ***therefore you will need to ensure that adequate exposure to RP112273 was achieved in a full battery of nonclinical studies, including chronic toxicity, reproductive and developmental, and carcinogenicity studies, in two species***.

PX 42 at -087.

56. In its response to **Question 3**, the FDA also informed Celgene that it could not rely on the "total agonist" approach to measuring metabolite exposure, an approach Celgene had attempted. Under this approach, Celgene had tried to add up the exposures of multiple compounds, including 2273, in order to reach a combined exposure multiple above the FDA-required threshold of 1.0 for the toxicology studies—because the exposure of 2273 alone did not satisfy the 1.0 threshold. *Id.*; *see also* PX 71 at -009 (November 8, 2017 Meier-Davis email to Jacobson-Kram stating: "As you know, in the two-year carc study . . . the exposure multiple is 0.7. Because RP112273 is the predominant analyte in humans, I'm thinking of additional scientific justification for the clinical exposure multiples relative to the 2-year carc. . . . [T]he clinical exposure multiple

was calculated [by] . . . summing the exposure for each of the three analytes in the nonclinical studies . . . . Using this approach, the estimated exposure multiple . . . gives a multiple greater than one (almost five).”). The FDA further stated that while Celgene had included mostly “***estimated***” nonclinical exposure multiples in the Briefing Book, ***actual*** “toxicokinetic data to document that RP112273 has been adequately assessed in the nonclinical studies” was required for the submission. PX 42 at -087.

57. In the Preliminary Meeting Comments, the FDA further stated that Celgene needed to include in the NDA full clinical study reports (“CSRs”), including bioanalytical validation reports, for all relevant Ozanimod pharmacokinetic (“PK”) and pharmacodynamics (“PD”) studies. In response to **Question 4**, which asked, “Does the Agency agree that the overall proposed clinical pharmacology package, including the additional information planned to be provided early in the NDA review, is acceptable and support the filing for the registration of ozanimod?”, the FDA explicitly responded: “***No***. A ***complete*** clinical pharmacology package, including all relevant PK and PD studies and population PK and ER analyses is required at the time of submission.” PX 42 at -087. The FDA further stated that “***[f]ull [Clinical Study Reports] (including the bioanalytical and validation reports) for [the 1001 Study] and all relevant clinical PK and PD studies are needed at the time of the NDA submission***.” *Id.*

58. The “bioanalytical and validation reports” that the FDA referenced in its response to Question 4 included LTS data. *See* PX 43 at 85 (Houn testifying: “Q: Is it your understanding that bioanalytical and validation reports would include long-term stability data? . . . A: I would agree with that.”); PX 41 ¶ 73; PX 44 ¶ 26.

59. In its November 21, 2017 Preliminary Meeting Comments, the FDA also stated that Celgene needed to submit 2273 LTS data for the RPC01-1001, RPC01-1904, RPC01-1906,

RPC01-301, and RPC01-201B clinical studies in the Ozanimod NDA. In response to **Question 5**, which asked, "Does the Agency agree with Celgene's proposed timing for the bioanalytical data package for the recently-identified major active metabolite RP112273?", the FDA instructed Celgene as follows:

> Include the Validation and Analytical Study Reports for all major metabolites in the CSRs [clinical study reports] for all relevant PK and PD studies. ***These reports must be available at the time of the NDA submission***.
>
> State whether fresh or retained plasma samples were used to quantify RP112273 in the relevant clinical studies, including RPC01-1001, RPC01-1904, RPC01-1906, RPC01-301, and RPC01-201B). ***If you used retained plasma samples to quantify RP112273 in the relevant Phase 1 studies, you will need to provide evidence that demonstrates the stability of RP112273 in human plasma at the time of the NDA submission***.

PX 42 at -088.

60. The FDA's Preliminary Meeting Comments were reviewed by Martin, Smith, Curran, Lamb, Backstrom, and Saillot, among others. PX 127 at -283. By November 22, 2017, Celgene had decided to cancel its pre-NDA meeting with the FDA, which "surprised" Lamb (PX 107 at 129) and which he found "[f]rustrating" (PX 146), and that Lamb described as a "***significant mistake***." PX 128 (Lamb writing, after Celgene received the RTF letter: "[T]he team's decision to not meet with review division was a ***significant mistake***. It was ***critical*** that we met with them to establish the path forward and to get a sense of how much they might be willing to work with us.").

61. Celgene knew that it needed up to 1,162 days of LTS data for the Metabolite to cover the samples from the studies that it planned to submit with its Ozanimod NDA filing. On November 21, 2017, Tran sent an email to Wilson with the subject "Urgent - FDA response," asking Wilson when he could "talk . . . regarding the response." PX 77 at -224. The next day, November 22, 2017, Tran asked Wilson "how much (if any) [of the data] in [Studies] 1904 and

1906 would be within the validated LTS" at the time of the submission. *Id.* at -223. Wilson responded: "***None of the 1904/1906 are within stability. We need between a year to almost 2 years to cover the studies***." *Id.* In a follow-up email, Tran asked Wilson to "create a table showing the required LTS and when [Celgene would have the LTS data] for each of these studies." *Id.* The table that Wilson created for Tran showed that Celgene needed between 382 and 1,162 days of LTS data to cover the 1904, 1906, 1001, and 201B studies. *Id.* at -226.

62. After receiving and reviewing the FDA's Preliminary Meeting Comments, Celgene personnel expressed concern about the consequences of submitting an incomplete NDA, including an RTF.

63. On November 26, 2017, Lamb sent an email to Gerald Masoudi, Celgene's General Counsel, with the subject "Ozanimod FDA Pre-NDA Meeting," stating:

> In the response to Question 5, FDA states that we will need to provide evidence that demonstrates the stability of RP112273 in human plasma at the time of the NDA submission if we used retain [sic] samples to quantify the RP112273 metabolite in the phase 1 studies. We have some stability data for plasma samples, but some of the studies are 2 to 3 years old and it is very unlikely that we have stability on plasma samples for that long.

PX 72.

64. On November 27, 2017, Lamb asked Houn to review the FDA's Preliminary Meeting Comments, noting that he was assembling a "tracker" memo to "help capture key gaps/challenges/etc related to the submission to ensure there is improved transparency and understanding of what will be included in the submission" and that he had "told Philippe [Martin] last week that [he] wanted to work on such a document . . . ." PX 73 at -858. Houn responded to Lamb's email about the FDA's Preliminary Meeting Comments, stating: "Well, no surprise." *Id.* at -857. Houn continued:

> ***I hope we do NOT submit without all the info as the risk for RTF is real. FDA has warned us. An RTF letter would state: "… on Nov. 21, 2017, we stated you must submit these data with the NDA*** . . ."
>
> . . . .
>
> ***In the grid, I recommend changing "Potential RTF issue" to "RTF issue". The FDA used "must submit with the NDA" for the missing info***. . . . I know this is a company disappointment but hopefully we don't compound our situation.

Id. Houn testified that she also discussed her concerns about the NDA submission with Backstrom. PX 43 at 119.

65. On November 28, 2017, after receiving Houn's comments, Lamb emailed Backstrom and Palmisano about documenting the deficiencies in the NDA:

> Attached is a document that I have started to populate outlining ***data gaps, potential review challenges that could impact labelling and/or approvability and potential refusal to file concerns for the upcoming ozanimod RMS submissions***. ***Creation of this document follows a number of discussions with Terrie [Curran]*** with a goal of ensuring this information is appropriate [sic] captured and that franchise leadership and senior management have visibility and there is transparency leading up to the submission decision. . . . .
>
> The goal is to ensure we have as much transparency as possible around the program risks/challenges going into both the NDA and MAA submissions.

PX 74 at -373.

66. Backstrom responded to Lamb later that day following a discussion with Smith, stating:

> Thank you for taking the lead on this assessment. ***I spoke to Scott [Smith] and informed him of our discussions*** and of the effort to do a risk assessment with respect to quality of the application, ***potential RTF issues and my recommendation that we (you and me along with Terrie) provide this to Mark [Alles] and Scott [Smith] in advance of submitting the application***. I also highlighted the value of the [Priority Review Voucher] and that this could mitigate any delay in the approval timelines if we need some additional time for the submission.

Id. at -372.

67. Lamb's "tracker" memo stated that the need to include the bioanalytical validation reports for all major metabolites in the PK and PD clinical study reports in the NDA at the time of submission—including LTS data for 2273—was a potential "***Refusal to File*** issue." PX 7 at -778-79. Lamb sent his memo to Backstrom and Curran, among others. *Id.* Curran emailed a copy of the memo to Smith on November 28, 2017 and stated: "I met with a small team this morning to review the FDAs feedback and will meet later today with the IIEC. Matt will be putting together a document [ ] to document the status of the submission, and mitigation of outstanding issues. ***I'll update you in person***." PX 6 at -727.

68. Lamb subsequently sent an updated version of the tracker memo to Backstrom, Curran, and others on December 1, 2017. PX 75. This version indicated that the "Regulatory Impact" of both the need to include the validation reports and the need to include 2273 LTS data was a "***Refusal to File issue***." *Id.* at -790. With respect to the need for LTS data for 2273, the memo stated: "Refusal to File issue and/or review matter depending on the amount of data available in the submission." *Id.*

69. On November 30, 2017, Lamb emailed Saillot, Backstrom, Tran, and Kao as follows:

> If we have almost 4-month stability at the time of NDA submission and amend the application during the review around the 8 month time point with additional data, we will have roughly 12-month sample stability in the NDA to support the RP112273 results from the impacted studies. Do we have a gap with samples from some studies being older than the stability that will be in the NDA and if so, which specific studies are impacted?

PX 76 at -212.

70. In response to Lamb's email, Tran summarized the LTS information Wilson had previously provided him on November 22, 2017, including that Celgene required more than one to two years of LTS data to cover the Phase I clinical studies:

> For the NDA, [11]2273 data are presented in 3 Clin Pharm studies and the Phase 3 studies (exposure-response analysis). Below is the table showing the ***required long-term stability (LTS) for these studies***. For the NDA, we have 4-month stability data. We plan to generate LTS data for 6, 12, 18, 24, 36, and 48 months on an ongoing basis.

Study	**Maximum Samples Storage (Days)**	**When RP112273 LTS Ready**
RPC01-1904 (hepatic impairment)	508	Dec-2018
RPC01-1906 (renal impairment)	382	Aug-2018
RPC01-1001 (PK in RMS)	393	Aug-2018
Phase 3 RPC01-201B, RPC01-301	1162	Sep-2020

PX 76 at -211; *see also* PX 77.

71. Celgene's external consultants expressed concerns about the Ozanimod NDA submission. In a July 20, 2017 email to Tran sent during the meeting with some of these consultants (and subsequently forwarded to Saillot, Martinborough, and Meier-Davis), Jacobson-Kram stated: "I did not want to interrupt the discussion but in looking at FDA guidance, there is a new twist." PX 48. Jacobson-Kram then quoted the portion of the FDA ICH M3(R2) Q&A guidance calling for safety multiples of 1.0 or greater when a metabolite such as 2273 composes the majority of total human exposure: "In some cases, for example when a metabolite composes the majority of the total human exposure, it is appropriate for exposure to the metabolite in animals to exceed that in humans . . . . In this latter case it is important to achieve a higher exposure to the metabolite in animals because this metabolite constitutes the bulk of human exposure." *Id.* Jacobson-Kram told Tran to "[p]lease mention this to the group." *Id.*

72. In an August 1, 2017 email to Meier-Davis, Jacobson-Kram raised the possibility that Celgene would need to "repeat an entire M3 package [of toxicology studies] for RP 112273" and further stated: "Unfortunately, you are dealing with a very conservative [FDA] division and they MAY consider Ozanimod to be a prodrug and ***coverage is needed in all species tested***." PX 38.[4] Three weeks later, in an August 23, 2017 email to Meier-Davis, Jacobson-Kram once again referenced the likelihood that the FDA would consider Ozanimod to be a prodrug, necessitating additional toxicology studies, stating: "The risk is [the FDA] may consider ozanimod to be a prodrug; that may require that RP112273 be studied at higher exposures." PX 50 at -012.

73. In a November 10, 2017 email to Meier-Davis, which was forwarded to Martin, Saillot, Tran, Thomas, Aranda, Kao, Skolnick, and Martinborough, among others, Jacobson-Kram identified the "issues" he believed the FDA would raise with respect to the Ozanimod NDA submission, describing these issues as "***the major push back that you can expect from FDA***." PX 51 at -940-41. Among the issues that Jacobson-Kram identified was the following:

> [T]he [ICH M3(R2)] guidance was designed to assure safety of metabolites of the API. In this particular instance RP112273 represents the overwhelming majority of drug related material and is responsible for the overwhelming majority of pharmacological activity. ICH M3(R2) states: "In some cases, for example when a metabolite composes the majority of the total human exposure, it is appropriate for exposure to the metabolite in animals to exceed that in humans (see also Question 12). In this latter case it is important to achieve a higher exposure to the metabolite in animals because this metabolite constitutes the bulk of human exposure." ***However, in the case of the rat carcinogenicity study and the segment 2 reproductive toxicology studies [Celgene] has less than the clinical [i.e., human] exposure for RP112273. Does the sponsor consider RP112273 to have be [sic] adequately tested in these studies?***

---

[4] A prodrug is a biologically inactive medication that is metabolized by the body into an active drug. *See* PX 49 at 46 ("Q: And do you have an understanding as to what a prodrug is? A: Generally it's a precursor molecule that is metabolized in the body such that the parent doesn't have pharmacologic activity, but the metabolites are the basis for the drug's efficacy.").

Id. at -940. Jacobson-Kram again referenced the possibility that Ozanimod could be considered a prodrug and the possibility that the FDA would require Celgene to "dose animals with RP112273," i.e., conduct new toxicology studies. *Id.*

74. On November 22, 2017, Meier-Davis forwarded the FDA's Preliminary Meeting Comments to Jacobson-Kram, and asked: "Could you review and provide your input on what studies are at risk and whether we should initiate at risk?" PX 52 at -655. In his November 23, 2017 response, which Meier-Davis forwarded to Martin on November 26, 2017, Jacobson-Kram wrote: "***As I pretty much expected, they didn't go for the 'total agonist' concept. The major message appears to be that they want actual data for metabolites, not estimated levels. So as we expected, the major challenge will be the rat carc study***." *Id.*

75. On November 16, 2017, Saillot emailed another consultant, Dr. James MacDonald ("MacDonald"), with a "run-down of the ongoing activities" with respect to the Metabolite and the NDA submission and stated, "you and I can discuss where you may be able to help us the most." PX 67 at -463-64. Saillot further stated: "The bottomline anyway will be whether FDA buys our 'total active structurally similar' approach . . . and if not and they require more [nonclinical] tox[icology] work, whether a post marketing commitment will suffice. Some folks mention that FDA's willingness to accept post-marketing commitment for these types of issue[s] is less than in the past." *Id.* at -464.

76. On November 16, 2017, Saillot provided MacDonald with copies of the Briefing Book and the draft Toxicology Written Summary for the NDA submission and asked for MacDonald's "reactions/suggestions." *Id.* at -462. After a telephone call, Saillot followed up with MacDonald on November 19, 2017 by sending him "some of the comments [he] provided on the . . . non-clinical overview" section of the NDA. *Id.* at -460-61. MacDonald emailed Saillot

his response to these comments later that day. *Id.* With respect to Saillot's statement that "[t]he late discovery of RP112273 has had an impact on the non-clinical safety evaluation of ozanimod," MacDonald stated: "***A clear acknowledgement of this and the resulting deficiencies in the package will enhance the credibility of the submission***." *Id.* at -460. With respect to Celgene's claim in the Briefing Book that the nonclinical safety multiples for RP112273 "are mostly above 1, and approach 1 . . . , which would be consistent with the ICH M3 guidance," MacDonald stated: "This is the kind of argument that is a '***red flag***' to me. . . . ***The simple fact is that you have no exposure multiple to this major metabolite and you should simply acknowledge that***." *Id.*

77. As MacDonald explained at deposition, Celgene's representation to the FDA that the exposure multiples for the Metabolite were adequate was "the sort of argument that [FDA] reviewers respond to and that diminishes the credibility of the argument that the sponsor is trying to make, because ***the data simply doesn't support the statement***." PX 68 at 59. MacDonald further testified:

> "[T]he data they [i.e., Celgene] have, the tables that they presented for review that are in the NDA ***show quite clearly that there is no exposure multiple***. It's not greater than one to this major metabolite in any of the species frankly, of the no effect dose, and so you just acknowledge that. . . . [T]he red flag is that you're not trying to deal directly with the data."

Id. at 60.

78. Saillot forwarded MacDonald's comments to Martin on November 19, 2017, stating:

> None of the comments from regulatory (including me, David, Tim and Matt) recommending stating exposure multiples including RP112273 and making the conclusions of each section consistent with the wording of the label have been taken into consideration . . . . The current text and positioning is at best confusing and at worse misleading and lacks credibility. **I am now at a stage where I am very concerned about the approvability of the NDA unless these issues are addressed**.

PX 129 at -539 (emphasis in original).

79. On November 29, 2017, Saillot provided MacDonald with the text of the FDA's response to the nonclinical question (Question 3) from the Preliminary Meeting Comments. PX 69 at -533. MacDonald responded to Saillot later that day: "An ***expected*** ***response*** from the Agency. ***The ominous wording I see is that the metabolite will be 'a review issue***'." *Id.* at -532-33. As MacDonald explained at his deposition, the FDA's use of "review issue" was ominous because "[a] review issue is FDA code word or code phrase for we don't agree with your position, and unless you give us something different, we are not going to accept your argument." PX 68 at 71; *see supra* ¶ 16 (discussing review issues). Thus, MacDonald further testified, "they were going to have a difficult time convincing the agency with the existing data that they had adequately characterized and complied with regulatory expectations." *Id.*

80. On November 30, 2017, Saillot sent MacDonald a draft of the Nonclinical Overview section of the NDA filing for his review. PX 69 at -531. MacDonald sent Saillot his comments to the draft section on December 3, 2017 and noted the following in the cover email: "***The document seems to suggest that everything is OK and the [compound] and metabolites have been well characterized. The data simply don't support that statement and I think it will elicit a negative response in the mind of at least the [FDA] pharm-tox reviewer***." *Id.* at -530-31. MacDonald took issue with a statement in the draft NDA filing suggesting that the Metabolite had been adequately assessed in non-clinical testing, stating: "Same comment as earlier – ***this metabolite has not been adequately evaluated by conventional rules of engagement and I believe this will elicit a negative response***." *Id.* at -557. MacDonald elaborated that RP112273 had not been qualified due to the inadequate exposure multiples for the toxicology tests and rejected Celgene's representation to the contrary: "Not sure how you [can] say this [i.e., that 2273 was

"qualified relative to repeated dose toxicity"] as the E[xposure] M[ultiple] in the carc and reprotox studies is <1 – ?" *Id.* at -541.

81. Saillot forwarded MacDonald's comments to Martin later that day. PX 70. MacDonald also forwarded his response to one of his colleagues, stating that "Jean-Louis [Saillot] and Receptos have a problem—but their FDA/draft NDA docs only show an 'arm-waving' approach to dealing with the problem. Not the sort of client we want to be spending this much time with!" PX 69 at -530.

82. At his deposition, MacDonald testified that Celgene "clearly had a problem." PX 68 at 151. As MacDonald explained:

> They [Celgene] were coming right into the firestorm of concern and regulatory circles around human specific metabolites and the [MIST] guidance; it's a white hot area of focus, and how can you rise above that and have a productive conversation about whether or not this molecule can be used safely in patients. . . . The issue of metabolites and differential exposures to metabolites, human specific metabolites is an area of intensive focus; it has been for the last ten -- five, ten years. And unfortunately, ozanimod landed right in the middle of that. So it was clear to me when I saw it, that is why I said they had a problem, I referred to that in several of my e-mails, when I said they had a problem, it was recognizing the heightened awareness at the agency of this issue, and they needed to have a very credible way to address it.

Id. at 151-52.

K. Ignoring the Negative FDA Feedback, Celgene Knowingly Submitted the NDA with Deficient Metabolite Data on December 22, 2017

83. When Celgene submitted the Ozanimod NDA on December 22, 2017, Defendants knew that generic versions of Gilenya, another treatment for MS, were set to hit the market in late 2019. PX 130 at 14; PX 131.

84. Defendants also knew that Celgene needed the revenues from Ozanimod to replace the revenues that it would lose when Revlimid's patent protection expired. *See* Defendants'

Answer (D.E. 220) ¶ 1; PX 132 at -118 (stating that "[m]aximiz[ing] peak sales of ozanimod" will "[a]ddress[] Revlimid loss of revenue through genericization").

85. Celgene's announcement on October 19, 2017 that it was scrapping development of GED-0301, its development-stage ulcerative colitis and Crohn's Disease drug, *see* PX 133, and its dramatic reduction in its Otezla sales guidance on October 26, 2017 (TAC ¶¶ 427-37), heightened the importance of Ozanimod to Celgene's future financial success. *See* PX 134 ("Revlimid will eventually lose patent protection, and the company has been aggressively looking to expand its business and diversify. . . . Celgene executives said that ozanimod could have peak annual sales of $4 billion to $6 billion and would complement GED-0301 and also Otezla . . . ."); PX 135 (Canaccord: "Despite the likely termination of the GED-0301 program. . . . [w]e continue to expect positive data from the Phase 3 RADIANCE study in MS for ozanimod at ECTRIMS, which should bolster ozanimod's approval prospect (***NDA submission for RMS expected by YE17***"); PX 136 (Benzinga reporting that Baird Equity Research stated that "***pressure to succeed in I&I . . . is now almost exclusively on ozanimod***"); PX 137 (BTIG: "Celgene reported 3Q results that severely disappointed relative to expectations on Otezla . . . . [T]he company is heavily dependent on pulling a trifecta with Ozanimod across MS, UC and CD."); PX 138 (Cantor Fitzgerald: "We had believed that pipeline execution would see CELG shares through the loss of REVLIMID, but the company's revisitation of guidance in the wake of GED-0301's failure creates an overhang and perhaps places greater pressure to execute on a strategic/business development option.").

86. Celgene employees, including Defendants Martin, Smith and Curran were entitled to receive bonuses if the Ozanimod NDA was submitted by year-end 2017. *See* PX 139 (listing "Submit NDA for Ozanimod in MS by end of 2017" as "result[] expected" to receive target bonus

under Management Incentive Plan); PX 140 (2017 proxy statement indicating that Smith was entitled to performance award based in part on the "filing of a new drug application"); PX 2 at 307 (Martin testifying that filing the Ozanimod NDA by year-end 2017 was "one of the factors for my performance . . . so it had an impact on my bonus"); *see also* PX 141 (identifying "NDA submission of Ozanimod on or before December 31, 2017" as "Milestone 1" entitling listed employees to bonuses of up to $50,000); PX 142 at 36 (Thomas testifying that she received a $50,000 bonus in connection with the filing of the Ozanimod NDA in 2017); PX 143 at 185 (Kao testifying that he was entitled to a $50,000 bonus upon submission of the Ozanimod NDA by year-end 2017).

87. Defendants were motivated to file the NDA in December 2017 for reasons unrelated to the regulatory sufficiency of the submission. Houn testified as follows:

> Q: So there really wouldn't be any purpose in submitting an NDA that gets rejected by the FDA, would there be? . . .
>
> A: Well, there are ***non-regulatory*** purposes. It doesn't serve regulatory, because this is a black mark on the company. But there are obviously non-regulatory considerations that are outside of my purview. . . . I don't know all the other non-regulatory considerations that [management] has to factor in. For me, I just give out what I think is my best regulatory advice, but [Backstrom] is a [Chief Medical Officer] and he's in the leadership team with the other folks at Celgene that I believe they have their own goals that was non-regulatory.
>
> Q: So do you think it was a goal of the company to not get the drug approved?
>
> A: I think it was a goal of the company to get the submission in. I think that might have been a -- you know, I'd have to go back or you would have to go back and look at what were the leadership goals for, you know, milestones to meet for personnel.

PX 43 at 161-63.

88. At the time of Celgene's January 8, 2018, January 25, 2018, and February 7, 2018 public statements, Defendants knew that the NDA—filed on December 22, 2017—suffered from both clinical and non-clinical deficiencies.

89. The clinical component of Celgene's Ozanimod NDA was deficient because Celgene failed to provide LTS data necessary to validate the 2273 samples from the clinical studies submitted as part of the NDA. Celgene submitted only 136 days of LTS data for 2273 in the NDA. PX 78 at -920. This 136 days of LTS data did not cover ***any*** of the samples from the RPC01-1904, RPC01-1905, and RPC01-1906 Phase I clinical pharmacology studies, or ***any*** of the samples from the RPC01-201B and RPC01-301 Phase III clinical pharmacology studies. In addition, the data covered only 194 of the 876 samples (or 22%) from the RPC01-1001 Phase I clinical pharmacology study. *See* PX 9 ¶¶ 99-100; PX 41 at ¶¶ 65, 81-82; *see also* PX 79, PX 80, PX 81, PX 82, PX 83, PX 84 (indicating the "Stored Days" for the samples from the RPC01-1904, RPC01-1905, RPC01-1906, RPC01-1001, RPC01-201B, and RPC01-301 studies).

90. The non-clinical component of Celgene's December 22, 2017 Ozanimod NDA was also deficient in multiple respects.

91. ***First***, several of the non-clinical safety multiples from Celgene's toxicology studies were below the FDA-mandated threshold of 1.0 for disproportionate metabolites like 2273: (i) the non-clinical safety multiple for the 2-year carcinogenicity study in rats was **0.8** (PX 9 ¶ 93; *see also* PX 37 at -720, Table 28); (ii) the non-clinical safety multiple for the EFD study in rabbits was **0.03** (PX 9 ¶ 93; *see also* PX 37 at -720, Table 28); and (iii) the non-clinical safety multiple for the EFD study in rats was **0.1** (PX 85 ¶ 69; *see also* PX 37 at -720, Table 28).

92. ***Second***, all of the dose levels Celgene utilized in the Ozanimod 6-month mouse carcinogenicity study inappropriately exceeded the MTD. PX 9 ¶¶ 84, 95; *see also* PX 37 at -724; PX 38. As Dr. Guengerich explained, "[t]oxicity data obtained with mice treated above the MTD dose should not be used to calculate [a safety multiple]" because "any dose exceeding the MTD has some inherent toxicity." PX 9 ¶ 95. Indeed, in an August 1, 2017 email, Meier-Davis expressly

told Jacobson-Kram not to consider the safety multiple from the 6-month mouse carcinogenicity study because the dose used to generate that multiple exceeded the MTD. PX 38 ("Note: the [6-month] mouse transgenic was above MTD, so don't include that in your evaluation."); *see also* PX 49 at 29 (testifying that dose used to calculate safety multiples must be below the MTD: "***What I should have included there is at a dose that didn't exceed the MTD. So that would be the level that was seen at a dose that didn't exceed the maximum tolerated dose, which can also be the NOAEL***.").

93. ***Third***, at the time of the NDA submission, several of the non-clinical safety multiples that Celgene reported in the submission were merely estimated figures because Celgene did not have actual, ***validated*** exposure data for certain of the animal species. *See* PX 9 ¶ 92; *see also* PX 86 at 223-25, 226; PX 37 at -692; *id.* at -725 (referencing the "estimated RP112273 exposure in the repeated dose toxicity study in rat and monkey, rat carcinogenicity, and rat embryo-fetal development studies"); *see also id.* at -720, Table 28 n.b ("Preclinical species exposure based on the quotient of the analyte exposure concentration from non-GLP and GLP studies."); *see also* PX 68 at 68 ("You need to have a chemical identification of the molecule rather than something that is estimated from differences on a chromatogram; I'm not sure how they estimated that. But the expectation in the field is that you have a measurement of the actual chemical entity with an assay that can be demonstrated to appropriately measure that."); *id.* at 116 ("It's my experience usually they would be based on ***actual validated assays***.").

L. On February 23, 2018, the FDA Issued the RTF Due to Insufficient Metabolite Data—the Exact Data Deficiencies the FDA Had Flagged, but Celgene Had Ignored, Prior to the NDA Filing

94. The FDA issued an RTF on February 23, 2018 and refused to file the Ozanimod NDA submission. PX 78. There were two bases for the RTF: deficiencies with the clinical data

(incomplete LTS data), and deficiencies with the non-clinical data (inadequate safety multiples in toxicology studies). As the RTF stated:

> ***The long-term stability of RP112273***, a recently identified predominant and active metabolite of ozanimod, ***has not yet been established***. Retained plasma samples were used to quantify RP112273 in studies RPC01-201 (Part A and B), RPC01-301, RPC01-1904, RPC01-1906 and for most of subjects in study RPC01-1001. ***The samples were analyzed outside of the long-term stability window (136 days) for RP112273***. . .

Id. at -920.

95. The RTF further stated:

> RP112273, an active metabolite with potency at the S1P 1 and 5 receptors similar to that of the parent compound, accounts for the majority (~90%) of drug-related material in circulation in humans. ***Therefore, you will need to demonstrate that RP112273 has been assessed in a standard battery of nonclinical studies. . . . Based on a preliminary examination, the available TK data are insufficient to allow a determination of the adequacy of the safety assessment for RP112273***.

Id. at -921.

96. The post-RTF correspondence between Celgene and the FDA confirms that the FDA found Celgene's safety multiples for several of the non-clinical toxicology studies to be inadequate. The minutes from Celgene's April 3, 2018 Type A meeting with the FDA following the issuance of the RTF letter state: "[T]he plasma RP112273 exposures achieved in the mouse and rat carcinogenicity studies are ***not adequate***, in the absence of data indicating higher RP112273 exposures would not be tolerated or feasible to achieve. Therefore, studies (in two species) to assess the carcinogenic potential of RP112273 may be needed . . . ." PX 87 at -737; *see also* PX 85 ¶ 72. In its November 9, 2018 written responses to Celgene's August 29, 2018 meeting request, the FDA stated: "The preliminary data summarized in . . . the briefing package suggest there was ***insufficient exposure*** to both [CC112273 and CC1084037] metabolites in the embryofetal development (EFD) and carcinogenicity studies in rat." PX 88 at -336; *see also* PX 85 ¶ 73.

97. The FDA's issuance of RTF letters are rare. According to data from the subscription data service BioMedtracker, the FDA issued just forty-five RTF letters in connection with NDA applications in the sixteen-plus years between December 31, 2001 and February 28, 2018. PX 144.

98. Celgene documents post-dating the Company's receipt of the RTF from the FDA confirm that Defendants knew that the NDA was deficient at the time it was submitted in December 2017. In a February 27, 2018 email to Backstrom and Palmisano, Lamb re-forwarded Tran's LTS chart from November 30, 2017 (*supra* ¶ 70), stating:

> ***Some of the studies are complete but we don't have the required sample stability for the RP112273 metabolite***. Please see the below table which provides dates for when we will have the required sample stability for some of the Clin Pharm studies in 2018. In the table you will see that we won't have the required stability data for the phase 3 samples until 2020. This is part of the equation. Once we have the stability data, we can consider the studies as "valid" as it relates to us having going back and used retain[ed] plasma samples for the RP112273 characterization.

PX 76 at -210. In this same email, Lamb acknowledged that the FDA never agreed to permit Celgene to supplement the NDA with LTS data following the submission in December 2017:

> ***FDA didn't agree to anything and they stated repeatedly that the CSRs [clinical study reports], BARs and stability data needed to be in the original submission.*** Even in a subsequent email exchange FDA stated reports needed to be submitted at [] the time of the NDA submission (not within 30 days which we proposed via email).

Id. at -209.

99. Tran corroborated Lamb's comments in a February 27, 2018 email to Palmisano. PX 45. Tran wrote: "[T]he FDA wanted LTS data and would not accept those during the NDA review. ***In the pre-NDA feedback, the FDA specifically requested LTS data for studies 1001 (PK/PD in RMS), 1904 (hepatic impairment) and 1906 (renal impairment)***." *Id.* at -976-77

100. On March 15, 2018, Faletto asked Lamb if he would address the audience at an upcoming Celgene Regulatory Affairs meeting. PX 95 at -840-41. Lamb responded:

> I will be happy to speak to ozanimod and the RTF in the opening and try to answer any questions folks may have. There isn't much to learn from a Regulatory Affairs perspective. ***FDA repeatedly stated what they expected, it was ignored and we got a RTF***.

Id. at -839.

101. On April 3, 2018, Curran gave a presentation to Celgene's Board of Directors describing the circumstances leading to the RTF. PX 96. One of the presentation slides, entitled "Ozanimod-Related Correspondence with the FDA," stated the following: "Feb 2018: . . . ***FDA issues Refusal to File Letter, identifying nonclinical and clin pharm deficiencies consistent with the pre-NDA meeting feedback***." *Id.* at -395.

102. Houn testified that she was not surprised by the RTF because the FDA had unambiguously told Celgene in November what was required at the time of the NDA submission. PX 43 at 109-11 ("Q: Dr. Houn, are you aware that Celgene received an RTF in response to its ozanimod New Drug Application in February of 2018? . . . A: Yes. Q: Were you surprised that Celgene received an RTF? A: No. Q: Why not? A: I wasn't surprised, because unless those studies were completed and put into the NDA, FDA had stated in November that, you know, that they are a requirement at the time of submission.").

M. Martin and Members of the Ozanimod NDA Team Regularly Furnished Smith and Curran with Information Regarding the Ozanimod NDA Process

103. In connection with each of his public statements regarding Ozanimod during the Class Period, Smith relied on information that he received from Martin and other members of the Ozanimod NDA team, and I&I leadership, including Curran. PX 147 at Response Nos. 13-17; PX 1 at 181.

104. In his role as Chief Operating Officer ("COO") and President of Celgene, Smith had the opportunity to review and comment on each of Celgene's Forms 10-Q, 10-K, and 8-K after these filings were reviewed by the franchise presidents. PX 1 at 39-40.

105. In his role as COO and President of Celgene, Smith participated in meetings with other members of management in advance of Celgene's quarterly earnings calls and investor presentations to discuss the topics that would be covered during the call and accompanying presentation, including "the important things for investors and others to know from the prior quarter," and reviewed the scripts and presentation slides for the call. *Id.* at 28, 30.

106. Martin provided information regarding Ozanimod to Curran in advance of Celgene's April 27, 2017 earnings conference call and slide presentation. PX 123.

107. Martin testified that it was "an important aspect of [his] job, to make sure that . . . Celgene was involved in the process in the decision-making process." PX 2 at 22.

108. Martin stated that his "main role" on the I&I Executive Committee ("IIEC") "was to make sure that the IIEC members [including Smith and Curran] were aware of what the project teams were doing." PX 2 at 32.

109. Martin explained that the role of the IIEC was to "ensure that the I&I franchise was well-managed." PX 2 at 29-30. Martin further explained with respect to the IIEC: "[I]t was a big component of communication to ensure that people are aware of what others are doing and, you know, also a[] way for us to know what else is going on at Celgene potentially to the head of IIEC would let us know if there were certain you know important strategic matters that were discussed within Celgene or other things that he felt we should know about, right. So a lot of it was communication." *Id.*

110. Saillot confirmed that Martin made presentations to the IIEC and that Martin updated the IIEC with respect to the Ozanimod NDA during 2017. PX 16 at 94-95. As Saillot further stated, Martin was "providing feedback to the IIEC" on the status of the NDA and "was definitely the voice of the group to the IIEC." *Id.* at 108-09.

111. Smith stated that he "relied . . . on information he received about Ozanimod from Philippe Martin." PX 148 at Response Nos. 2 and 3.

112. Martin testified that Curran would "ask [him] questions about Ozanimod on a regular basis," explaining that "she would call me when she would need something or send me an email." PX 2 at 56.

113. Martin further testified that "in the July [2017] timeframe," he had conversations with Curran about the mass balance data, explaining that these conversations were "part of the communication that was required for the organization to know about the metabolite and what we are going to do about it." PX 64 at 106-07.

114. Martin also provided information regarding the NDA submission to Lamb. For example, Lamb noted in a November 10, 2017 email to Jay Backstrom that he would ask Martin and Jean-Louis Saillot "early next week . . . that they share the FDA feedback as soon as it is received." PX 145.

115. Consistent with this email, on November 22, 2017, Martin circulated the FDA's November 21, 2017 Preliminary Meeting Comments to Lamb, Curran, and several other Celgene executives on November 22, 2017. PX 144.

116. After receiving the Preliminary Meeting Comments, Martin was involved in assessing the risks to the NDA submission and discussing those risks with Celgene's senior management. *See* PX 146 (Nov. 22, 2017 email from Lamb to Curran: "I think it would be great

if the Ozanimod team (at least Phillippe [Martin] if a few team members can't be pulled away) could present to the franchise leadership a risk assessment for the NDA assessing risks to submission timing, potential risks related to FDA filing the application (RTF issues), and review risks that could impact labeling and/or a first-cycle approval.").

N. The Ozanimod RTF and Delayed NDA Submission Negatively Impacted Celgene's Stock Price

117. In response to Celgene's disclosure on February 27, 2018 that it had received an RTF from the FDA regarding its Ozanimod NDA, the price of Celgene common stock fell from a close of $95.78 on February 27, 2018 to a close of $87.12 on February 28, 2018. PX 149 ¶¶ 28-32; PX 150 ¶¶ 40-47.

118. In response to the April 29, 2018 Morgan Stanley report entitled "More Bread Crumbs Yield Less Confidence In Ozanimod," which discussed a timeline of a one-to-three-year delay in Celgene's resubmission of the NDA based on newly acquired information regarding the concentration of the Metabolite and the need for additional studies, Celgene's common stock fell from a close of $91.18 per share on Friday, April 27, 2018 to a close of $87.10 per share on Monday, April 30, 2018. PX 149 ¶¶ 33-35; PX 150 ¶¶ 48-56.